

5 Claims

1. An isolated protein having anticoagulant activity and having one or more NAP domains, wherein each NAP domain includes the sequence:

Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-  
10 Cys-A9-Cys-A10 [FORMULA II], wherein

(a) A1 is an amino acid sequence of 7 to 8 amino acid residues;

(b) A2 is an amino acid sequence;

(c) A3 is an amino acid sequence of 3 amino acid  
15 residues;

(d) A4 is an amino acid sequence;

(e) A5 is an amino acid sequence of 3 to 4 amino acid residues;

(f) A6 is an amino acid sequence;

(g) A7 is an amino acid residue;  
20

(h) A8 is an amino acid sequence of 11 to 12 amino acid residues;

(i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and

(j) A10 is an amino acid sequence;  
25

wherein each of A2, A4, A6 and A10 has an independently selected number of independently selected amino acid residues and each sequence is selected such that each NAP domain has in total less than about 120 amino acid  
30 residues.

2. The protein of claim 1, wherein A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are independently selected amino acid residues.  
35

3. The protein of claim 1, wherein A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> is selected from the group consisting of Ala, Arg, Pro, Lys, Ile, His, Leu, and Thr, and A3<sub>b</sub> is selected from the group consisting of Lys, Thr, and Arg.  
40

- 5        4.    The protein of claim 3, wherein A3 is selected  
from the group consisting of  
         Glu-Ala-Lys,  
         Glu-Arg-Lys,  
         Glu-Pro-Lys,  
10       Glu-Lys-Lys,  
         Glu-Ile-Thr,  
         Glu-His-Arg,  
         Glu-Leu-Lys, and  
         Glu-Thr-Lys.
- 15       5.    The protein of claim 1, wherein A4 is an amino  
acid sequence having a net anionic charge.
- 20       6.    The protein of claim 1, wherein A7 is Val.
7.    The protein of claim 1, wherein A7 is Ile.
8.    The protein of claim 1, wherein A8 includes the  
amino acid sequence A8<sub>a</sub>-A8<sub>b</sub>-A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> [SEQ. ID.  
25 NO. 68], wherein  
       (a)   A8<sub>a</sub> is the first amino acid residue in A8,  
       (b)   at least one of A8<sub>a</sub> and A8<sub>b</sub> is selected from the  
group consisting of Glu or Asp, and  
       (c)   A8<sub>c</sub> through A8<sub>g</sub> are independently selected amino  
30 acid residues.
9.    The protein of claim 8, wherein  
       (a)   A8<sub>a</sub> is Glu or Asp,  
       (b)   A8<sub>b</sub> is an independently selected amino acid  
35 residue,  
       (c)   A8<sub>c</sub> is Gly,  
       (d)   A8<sub>d</sub> is selected from the group consisting of  
Phe, Tyr, and Leu,  
       (e)   A8<sub>e</sub> is Tyr,  
40       (f)   A8<sub>f</sub> is Arg, and  
       (g)   A8<sub>g</sub> is selected from Asp and Asn.

- 5        10. The protein of claim 9, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-  
A8<sub>g</sub> is selected from the group consisting of  
Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
10       Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].
11. The protein of claim 8, wherein  
(a) A8<sub>a</sub> is an independently selected amino acid  
15       residue,  
(b) A8<sub>b</sub> is Glu or Asp,  
(c) A8<sub>c</sub> is Gly,  
(d) A8<sub>d</sub> is selected from the group consisting of  
Phe, Tyr, and Leu,  
20       (e) A8<sub>e</sub> is Tyr,  
(f) A8<sub>f</sub> is Arg, and  
(g) A8<sub>g</sub> is selected from Asp and Asn.
12. The protein of claim 11, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-  
25       A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of  
Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
30       Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].
13. The protein of claim 8, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-  
A8<sub>g</sub> is selected from the group consisting of  
Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
35       Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].
- 40       14. The protein of claim 1, wherein A10 includes an  
amino acid sequence selected from the group consisting of  
Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],

5        Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
         Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
         Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

15        15. The protein of claim 14, wherein A10 includes  
10 the amino acid sequence Glu-Ile-Ile-His-Val [SEQ. ID. NO.  
74].

16. The protein of claim 15 having a NAP domain with  
an amino acid sequence substantially the same as that of  
15 AcaNAP5 [SEQ. ID. NO. 40] or AcaNAP6 [SEQ. ID. NO. 41].

17. The protein of claim 14, wherein A10 includes  
the amino acid sequence Asp-Ile-Ile-Met-Val [SEQ. ID. NO.  
75].

20

18. The protein of claim 14, wherein A10 includes  
the amino acid sequence Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID.  
NO. 76].

25        19. The protein of claim 14, wherein A10 includes  
the amino acid sequence Met-Glu-Ile-Ile-Thr [SEQ. ID. NO.  
77].

20. The protein of claim 1 derived from a nematode  
30 species.

21. The protein of claim 20, wherein said nematode  
species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
35 *duodenale*, *Necator americanus*, and *Heligomosomoides*  
*polygyrus*.

22. The protein of claim 1, wherein  
      (a) A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and  
40 A3<sub>b</sub> are independently selected amino acid residues;  
      (b) A4 is an amino acid sequence having a net  
anionic charge;

5 (c) A7 is selected from the group consisting of Val  
and Ile;

(d) A8 includes an amino acid sequence selected from  
the group consisting of

10 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73]; and

(e) A10 includes an amino sequence selected from the  
15 group consisting of

Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],  
Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
20 Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

23. The protein of claim 22 having a NAP domain  
substantially the same as NAP domains selected from  
AcaNAP5 [SEQ. ID. NO. 40] and AcaNAP6 [SEQ. ID. NO. 41].

25 24. The protein of claim 22 derived from a nematode  
species.

25. The protein of claim 24, wherein said nematode  
species is selected from the group consisting of  
30 *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
*duodenale*, *Necator americanus*, and *Heligomosomoides*  
*polygyrus*.

26. The protein of claim 1, wherein

35 (a) A3 is selected from the group consisting of  
Glu-Ala-Lys,  
Glu-Arg-Lys,  
Glu-Pro-Lys,  
Glu-Lys-Lys,  
40 Glu-Ile-Thr,  
Glu-His-Arg,  
Glu-Leu-Lys, and

5           Glu-Thr-Lys;

(b) A4 is an amino acid sequence having a net anionic charge;

(c) A7 is Val or Ile;

(d) A8 includes an amino acid sequence selected from  
10 the group consisting of

A8a-A8b-Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 78],

A8a-A8b-Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 79],

A8a-A8b-Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 80],

A8a-A8b-Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 81],

15 and

A8a-A8b-Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 82],  
wherein at least one of A8a and A8b is Glu or Asp;

(e) A9 is an amino acid sequence of five amino acid residues; and

20 (f) A10 includes an amino acid sequence selected from the group consisting of

Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],

Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],

Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and

25 Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

27. The protein of claim 26 having a NAP domain substantially the same as NAP domains selected from AcaNAP5 [SEQ. ID. NO. 40] and AcaNAP6 [SEQ. ID. NO. 41].  
30

28. The protein of claim 26 derived from a nematode species.

29. The protein of claim 28, wherein said nematode  
35 species is selected from the group consisting of *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

40 30. An isolated protein having Factor Xa inhibitory activity selected from the group consisting of AcaNAP5 [SEQ. ID. NO. 40] and AcaNAP6 [SEQ. ID. NO. 41].

5

31. An isolated recombinant cDNA molecule encoding a protein having Factor Xa inhibitory activity and having one or more NAP domains, wherein each NAP domain includes the sequence:

10 Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 [FORMULA II], wherein

(a) A1 is an amino acid sequence of 7 to 8 amino acid residues;

(b) A2 is an amino acid sequence;

15 (c) A3 is an amino acid sequence of 3 amino acid residues;

(d) A4 is an amino acid sequence;

(e) A5 is an amino acid sequence of 3 to 4 amino acid residues;

20 (f) A6 is an amino acid sequence;

(g) A7 is an amino acid residue;

(h) A8 is an amino acid sequence of 11 to 12 amino acid residues;

25 (i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and

(j) A10 is an amino acid sequence;

wherein each of A2, A4, A6 and A10 has an independently selected number of independently selected amino acid residues and each sequence is selected such that each NAP  
30 domain has in total less than about 120 amino acid residues.

32. The cDNA molecule of claim 31, wherein A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are  
35 independently selected amino acid residues.

33. The cDNA molecule of claim 31, wherein A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> is selected from the group consisting of Ala, Arg, Pro, Lys, Ile, His, Leu, and  
40 Thr, and A3<sub>b</sub> is selected from the group consisting of Lys, Thr, and Arg.

- 5        34. The cDNA molecule of claim 33, wherein A3 is  
selected from the group consisting of  
         Glu-Ala-Lys,  
         Glu-Arg-Lys,  
         Glu-Pro-Lys,  
10       Glu-Lys-Lys,  
         Glu-Ile-Thr,  
         Glu-His-Arg,  
         Glu-Leu-Lys, and  
         Glu-Thr-Lys.
- 15       35. The cDNA molecule of claim 31, wherein A4 is an  
amino acid sequence having a net anionic charge.
- 20       36. The cDNA molecule of claim 31, wherein A7 is  
Val.
37. The cDNA molecule of claim 31, wherein A7 is  
Ile.
- 25       38. The cDNA molecule of claim 31, wherein A8  
includes an amino acid sequence A8<sub>a</sub>-A8<sub>b</sub>-A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-  
A8<sub>g</sub> [SEQ. ID. NO. 68], wherein  
         (a) A8<sub>a</sub> is the first amino acid residue in A8,  
         (b) at least one of A8<sub>a</sub> and A8<sub>b</sub> is selected from the  
30       group consisting of Glu or Asp, and  
         (c) A8<sub>c</sub> through A8<sub>g</sub> are independently selected amino  
acid residues.
- 35       39. The cDNA molecule of claim 38, wherein  
         (a) A8<sub>a</sub> is Glu or Asp,  
         (b) A8<sub>b</sub> is an independently selected amino acid  
residue,  
         (c) A8<sub>c</sub> is Gly,  
         (d) A8<sub>d</sub> is selected from the group consisting of  
40       Phe, Tyr, and Leu;  
         (e) A8<sub>e</sub> is Tyr,  
         (f) A8<sub>f</sub> is Arg, and



- 5 (g) A8<sub>g</sub> is selected from Asp and Asn.

40. The cDNA molecule of claim 39, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of

- 10 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].

- 15 41. The cDNA molecule of claim 38, wherein

(a) A8<sub>a</sub> is an independently selected amino acid residue,

- (b) A8<sub>b</sub> is Glu or Asp,  
(c) A8<sub>c</sub> is Gly,  
20 (d) A8<sub>d</sub> is selected from the group consisting of  
Phe, Tyr, and Leu,  
(e) A8<sub>e</sub> is Tyr,  
(f) A8<sub>f</sub> is Arg, and  
(g) A8<sub>g</sub> is selected from Asp and Asn.

25

42. The cDNA molecule of claim 41, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of

- 30 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].

43. The cDNA molecule of claim 38, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of

- 35 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
40 Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].

5        44. The cDNA molecule of claim 31, wherein A10  
includes an amino acid sequence selected from the group  
consisting of

          Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],  
          Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
10        Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
          Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

          45. The cDNA molecule of claim 44, wherein A10  
includes the amino acid sequence Glu-Ile-Ile-His-Val [SEQ.  
15 ID. NO. 74].

          46. The cDNA molecule of claim 45 having a  
nucleotide sequence substantially the same as that coding  
for AcaNAP5 [SEQ. ID. NO. 3] or AcaNAP6 [SEQ. ID. NO. 5].  
20

          47. The cDNA molecule of claim 44, wherein A10  
includes the amino acid sequence Asp-Ile-Ile-Met-Val [SEQ.  
ID. NO. 75].

25        48. The cDNA molecule of claim 44, wherein A10  
includes the amino acid sequence Phe-Ile-Thr-Phe-Ala-Pro  
[SEQ. ID. NO. 76].

          49. The cDNA molecule of claim 44, wherein A10  
30 includes the amino acid sequence Met-Glu-Ile-Ile-Thr [SEQ.  
ID. NO. 77].

          50. The cDNA molecule of claim 31 derived from a  
nematode species.  
35

          51. The cDNA molecule of claim 50, wherein said  
nematode species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
*duodenale*, *Necator americanus*, and *Heligomosomoides*  
40 *polygyrus*.

          52. The cDNA molecule of claim 31, wherein

- 5 (a) A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and  
A3<sub>b</sub> are independently selected amino acid residues;
- (b) A4 is an amino acid sequence having a net  
anionic charge;
- 10 (c) A7 is selected from the group consisting of Val  
and Ile;
- (d) A8 includes an amino acid sequence selected from  
the group consisting of
- 15 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73]; and
- (e) A10 includes an amino sequence selected from the  
group consisting of
- 20 Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],  
Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].
- 25 53. The cDNA of claim 52 that is selected from cDNAs  
substantially the same as cDNAs coding for AcaNAP5 [SEQ.  
ID. NO. 3] and AcaNAP6 [SEQ. ID. NO. 5].
- 30 54. The cDNA molecule of claim 52 derived from a  
nematode species.
- 35 55. The cDNA molecule of claim 54, wherein said  
nematode species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
*duodenale*, *Necator americanus*, and *Heligomosomoides*  
*polygyrus*.
- 40 56. The cDNA molecule of claim 31, wherein  
(a) A3 is selected from the group consisting of  
Glu-Ala-Lys,  
Glu-Arg-Lys,  
Glu-Pro-Lys,

- 5           Glu-Lys-Lys,  
          Glu-Ile-Thr,  
          Glu-His-Arg,  
          Glu-Leu-Lys, and  
          Glu-Thr-Lys;
- 10       (b) A4 is an amino acid sequence having a net  
          anionic charge;  
          (c) A7 is Val or Ile;  
          (d) A8 includes an amino acid sequence selected from  
              the group consisting of
- 15           A8<sub>a</sub>-A8<sub>b</sub>-Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 78],  
          A8<sub>a</sub>-A8<sub>b</sub>-Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 79],  
          A8<sub>a</sub>-A8<sub>b</sub>-Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 80],  
          A8<sub>a</sub>-A8<sub>b</sub>-Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 81],  
          and
- 20           A8<sub>a</sub>-A8<sub>b</sub>-Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 82],  
          wherein at least one of A8<sub>a</sub> and A8<sub>b</sub> is Glu or Asp;  
          (e) A9 is an amino acid sequence of five amino acid  
              residues; and  
          (f) A10 includes an amino acid sequence selected
- 25       from the group consisting of  
          Glu-Ile-Ile-His-Val, [SEQ. ID. NO. 74]  
          Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
          Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
          Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].
- 30

57. The cDNA molecule of claim 56 that is selected  
from cDNAs coding for a NAP domain substantially the same  
as NAP domains selected from AcaNAP5 [SEQ. ID. NO. 40] and  
AcaNAP6 [SEQ. ID. NO. 41].

58. The cDNA molecule of claim 56 derived from a  
nematode species.

59. The cDNA molecule of claim 58, wherein said  
nematode species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
*duodenale*, *Necator americanus*, and *Heligomosomoides*

5 polygyrus.

60. A cDNA molecule encoding a protein having Factor  
Xa inhibitory activity selected from the group consisting  
of proteins having NAP domains substantially the same as  
10 AcaNAP5 [SEQ. ID. NO. 40] or AcaNAP6 [SEQ. ID. NO. 41].

61. A pharmaceutical composition comprising the  
protein of claim 1.

15 62. A pharmaceutical composition comprising the  
protein of claim 22.

63. A pharmaceutical composition comprising the  
protein of claim 26.  
20

64. A pharmaceutical composition comprising a  
protein selected from the group consisting of AcaNAP5  
[SEQ. ID. NO. 40] and AcaNAP6 [SEQ. ID. NO. 41].

25 65. A method of inhibiting blood coagulation  
comprising administering a protein of claim 1 with a  
pharmaceutically acceptable carrier.

66. A method of inhibiting blood coagulation  
30 comprising administering a protein of claim 22 with a  
pharmaceutically acceptable carrier.

67. A method of inhibiting blood coagulation  
comprising administering a protein of claim 26 with a  
35 pharmaceutically acceptable carrier.

68. A method of inhibiting blood coagulation  
comprising administering a protein selected from the group  
consisting of AcaNAP5 [SEQ. ID. NO. 40] and AcaNAP6 [SEQ.  
40 ID. NO. 41].

69. A protein of claim 1, wherein said protein has

5 two NAP domains.

70. A protein of claim 22, wherein said protein has two NAP domains.

10 71. A protein of claim 26, wherein said protein has two NAP domains.

72. A protein of claim 1 wherein said NAP domain includes the amino acid sequence:

15 Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10

wherein

(a) Cys-A1 is selected from SEQ. ID NOS. 67 and 156;

(b) Cys-A2-Cys is selected from one of SEQ. ID NOS.  
20 157 to 159;

(c) A3-Cys-A4 is selected from one of SEQ. ID. NOS.  
160 to 173.

(d) Cys-A5 is selected from SEQ. ID. NOS. 174 and  
175;

25 (e) Cys-A6 is selected from one of SEQ. ID. NOS. 176  
to 178;

(f) Cys-A7-Cys-A8 is selected from SEQ. ID. NOS. 179  
and 180;

(g) Cys-A9 is selected from one of SEQ. ID. NOS. 181  
30 to 183; and

(h) Cys-A10 is selected from one of SEQ. ID. NOS.  
184 to 204.

73. An isolated protein having anticoagulant activity and having one or more NAP domains, wherein each  
35 NAP domain includes the sequence:

Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 (FORMULA III),

wherein

(a) A1 is an amino acid sequence of 7 to 8 amino  
40 acid residues;

(b) A2 is an amino acid sequence;

(c) A3 is an amino acid sequence of 3 amino acid

5 residues;

(d) A4 is an amino acid sequence;

(e) A5 is an amino acid sequence of 3 to 4 amino acid residues;

(f) A6 is an amino acid sequence;

10 (g) A7 is an amino acid residue;

(h) A8 is an amino acid sequence of 11 to 12 amino acid residues;

(i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and

15 (j) A10 is an amino acid sequence;

wherein each of A2, A4, A6 and A10 has an independently selected number of independently selected amino acid residues and each sequence is selected such that each NAP domain has in total less than about 120 amino acid  
20 residues.

74. The protein of claim 73, wherein A3 has the sequence Asp-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are independently selected amino acid residues.  
25

75. The protein of claim 73, wherein A3 is Asp-Lys-Lys.

76. The protein of claim 73, wherein A4 is an amino  
30 acid sequence having a net anionic charge.

77. The protein of claim 73, wherein A5 has the sequence A5<sub>a</sub>-A5<sub>b</sub>-A5<sub>c</sub>-A5<sub>d</sub> [SEQ. ID. NO. 85], wherein A5<sub>a</sub> through A5<sub>d</sub> are independently selected amino acid  
35 residues.

78. The protein of claim 77, wherein A5<sub>a</sub> is Leu and A5<sub>c</sub> is Arg.

40 79. The protein of claim 73, wherein A7 is selected from the group consisting of Val and Ile.

5           80. The protein of claim 73, wherein A7 is Val.

81. The protein of claim 73, wherein A8 includes an amino acid sequence A8<sub>a</sub>-A8<sub>b</sub>-A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> [SEQ. ID. NO. 68], wherein

- 10           (a) A8<sub>a</sub> is the first amino acid residue in A8,  
             (b) at least one of A8<sub>a</sub> and A8<sub>b</sub> is selected from the group consisting of Glu or Asp, and  
             (c) A8<sub>c</sub> through A8<sub>g</sub> are independently selected amino acid residues.

15

82. The protein of claim 81, wherein

- (a) A8<sub>a</sub> is Glu or Asp,  
             (b) A8<sub>b</sub> is an independently selected amino acid residue,  
20           (c) A8<sub>c</sub> is Gly,  
             (d) A8<sub>d</sub> is selected from the group consisting of Phe, Tyr, and Leu,  
             (e) A8<sub>e</sub> is Tyr,  
             (f) A8<sub>f</sub> is Arg, and  
25           (g) A8<sub>g</sub> is selected from Asp and Asn.

83. The protein of claim 82, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70].

30           84. The protein of claim 81, wherein

- (a) A8<sub>a</sub> is an independently selected amino acid residue,  
             (b) A8<sub>b</sub> is Glu or Asp,  
             (c) A8<sub>c</sub> is Gly,  
35           (d) A8<sub>d</sub> is selected from the group consisting of Phe, Tyr, and Leu,  
             (e) A8<sub>e</sub> is Tyr,  
             (f) A8<sub>f</sub> is Arg, and  
             (g) A8<sub>g</sub> is selected from Asp and Asn.

40

85. The protein of claim 84, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70].



5

86. The protein of claim 73 derived from a nematode species.

87. The protein of claim 86, wherein said nematode species is selected from the group consisting of *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

15

88. The protein of claim 73, wherein

(a) A3 is has the sequence Asp-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are independently selected amino acid residues;

(b) A4 is an amino acid sequence having a net anionic charge;

20

(c) A5 has the sequence A5<sub>a</sub>-A5<sub>b</sub>-A5<sub>c</sub>-A5<sub>d</sub> [SEQ. ID. NO. 85], wherein A5<sub>a</sub> through A5<sub>d</sub> are independently selected amino acid residues, and

(d) A7 is selected from the group consisting of Val and Ile.

25

89. The protein of claim 88 having a NAP domain with an amino acid sequence substantially the same as the NAP domain of AcaNAPc2 [SEQ. ID. NO. 59].

30

90. The protein of claim 88 derived from a nematode species.

91. The protein of claim 90, wherein said nematode species is selected from the group consisting of *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

40

92. The protein of claim 73, wherein

(a) A3 is Asp-Lys-Lys;

(b) A4 is an amino acid sequence having a net anionic charge;

- 5 (c) A5 has the sequence A5<sub>a</sub>-A5<sub>b</sub>-A5<sub>c</sub>-A5<sub>d</sub>, wherein A5<sub>a</sub> is Leu, A5<sub>c</sub> is Arg, and A5<sub>b</sub> and A5<sub>d</sub> are independently selected amino acid residues [SEQ. ID. NO. 357],  
(d) A7 is Val; and  
(e) A8 includes an amino acid sequence A8<sub>a</sub>-A8<sub>b</sub>-Gly-  
10 Phe-Tyr-Arg-Asn [SEQ. ID. NO. 79], wherein at least one of A8<sub>a</sub> and A8<sub>b</sub> is Glu or Asp.

93. The protein of claim 92 having a NAP domain with an amino acid sequence substantially the same as the NAP  
15 domain of AcaNAPc2 [SEQ. ID. NO. 59].

94. The protein of claim 92 derived from a nematode species.

20 95. The protein of claim 94, wherein said nematode species is selected from the group consisting of *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

25 96. An isolated protein having Factor VIIa/TF inhibitory activity having a NAP domain with an amino acid sequence that is substantially the same as the NAP domain of AcaNAPc2 [SEQ. ID. NO. 59].

30 97. An isolated recombinant cDNA molecule encoding a protein having anticoagulant activity and having one or more NAP domains, wherein each NAP domain includes the sequence:

35 Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 [FORMULA III], wherein

- (a) A1 is an amino acid sequence of 7 to 8 amino acid residues;  
(b) A2 is an amino acid sequence;  
40 (c) A3 is an amino acid sequence of 3 amino acid residues;  
(d) A4 is an amino acid sequence;

- 5 (e) A5 is an amino acid sequence of 3 to 4 amino acid residues;  
(f) A6 is an amino acid sequence;  
(g) A7 is an amino acid residue;  
(h) A8 is an amino acid sequence of 11 to 12 amino  
10 acid residues;  
(i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and  
(j) A10 is an amino acid sequence;  
wherein each of A2, A4, A6 and A10 has an independently  
15 selected number of independently selected amino acid residues and each sequence is selected such that each NAP domain has in total less than about 120 amino acid residues.

20 98. The cDNA molecule of claim 97, wherein A3 has the sequence Asp-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are independently selected amino acid residues.

25 99. The cDNA molecule of claim 97, wherein A3 is Asp-Lys-Lys.

100. The cDNA molecule of claim 97, wherein A4 is an amino acid sequence having a net anionic charge.

30 101. The cDNA molecule of claim 97, wherein A5 has the sequence A5<sub>a</sub>-A5<sub>b</sub>-A5<sub>c</sub>-A5<sub>d</sub> [SEQ. ID. NO. 85], wherein A5<sub>a</sub> through A5<sub>d</sub> are independently selected single amino acid residues.

35 102. The cDNA molecule of claim 101, wherein A5<sub>a</sub> is Leu and A5<sub>c</sub> is Arg.

40 103. The cDNA molecule of claim 97, wherein A7 is selected from the group consisting of Val and Ile.

104. The cDNA molecule of claim 97, wherein A7 is Val.

5

105. The cDNA molecule of claim 97, wherein A8 includes an amino acid sequence A8<sub>a</sub>-A8<sub>b</sub>-A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> [SEQ. ID. NO. 68], wherein

- (a) A8<sub>a</sub> is the first amino acid residue in A8,  
10 (b) at least one of A8<sub>a</sub> and A8<sub>b</sub> is selected from the group consisting of Glu or Asp, and  
(c) A8<sub>c</sub> through A8<sub>g</sub> are independently selected amino acid residues.

15

106. The cDNA molecule of claim 105, wherein

- (a) A8<sub>a</sub> is Glu or Asp,  
(b) A8<sub>b</sub> is an independently selected amino acid residue,  
(c) A8<sub>c</sub> is Gly,  
20 (d) A8<sub>d</sub> is selected from the group consisting of Phe, Tyr, and Leu,  
(e) A8<sub>e</sub> is Tyr,  
(f) A8<sub>f</sub> is Arg, and  
(g) A8<sub>g</sub> is selected from Asp and Asn.

25

107. The cDNA molecule of claim 106, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70].

30

108. The cDNA molecule of claim 105, wherein

- (a) A8<sub>a</sub> is an independently selected amino acid residue,  
(b) A8<sub>b</sub> is Glu or Asp,  
(c) A8<sub>c</sub> is Gly,  
(d) A8<sub>d</sub> is selected from the group consisting of  
35 Phe, Tyr, and Leu,  
(e) A8<sub>e</sub> is Tyr,  
(f) A8<sub>f</sub> is Arg, and  
(g) A8<sub>g</sub> is selected from Asp and Asn.

40

109. The cDNA molecule of claim 108, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70].

5           110. The cDNA molecule of claim 97 derived from a nematode species.

10           111. The cDNA molecule of claim 110, wherein said nematode species is selected from the group consisting of *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

15           112. The cDNA molecule of claim 97, wherein  
          (a) A3 has the sequence Asp-A3a-A3b, wherein A3a and A3b are independently selected amino acid residues;

          (b) A4 is an amino acid sequence having a net anionic charge;

20           (c) A5 has the sequence A5a-A5b-A5c-A5d, wherein A5a through A5d are independently selected amino acid residues [SEQ. ID. NO. 85], and

          (d) A7 is selected from the group consisting of Val and Ile.

25           113. The cDNA molecule of claim 112 having a nucleotide sequence coding for an amino acid sequence substantially the same as the NAP domain of AcaNAPc2 [SEQ. ID. NO. 59].

30           114. The cDNA molecule of claim 112 derived from a nematode species.

35           115. The cDNA molecule of claim 114, wherein said nematode species is selected from the group consisting of *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

40           116. The cDNA molecule of claim 97, wherein

          (a) A3 is Asp-Lys-Lys;

          (b) A4 is an amino acid sequence having a net anionic charge;

5 (c) A5 has the sequence A5<sub>a</sub>-A5<sub>b</sub>-A5<sub>c</sub>-A5<sub>d</sub> [SEQ. ID. NO. 129], wherein A5<sub>a</sub> is Leu, A5<sub>c</sub> is Arg, and A5<sub>b</sub> and A5<sub>d</sub> are independently selected amino acid residues,

(d) A7 is Val; and

(e) A8 includes an amino acid sequence A8<sub>a</sub>-A8<sub>b</sub>-Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 79], wherein at least one of A8<sub>a</sub> and A8<sub>b</sub> is Glu or Asp.

117. The cDNA molecule of claim 116 having a nucleotide sequence which codes for an amino acid sequence  
15 substantially the same as AcaNAPc2 [SEQ. ID. NO. 59].

118. The cDNA molecule of claim 116 derived from a nematode species.

20 119. The cDNA molecule of claim 118, wherein said nematode species is selected from the group consisting of *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

25 120. An isolated cDNA molecule encoding a protein having Factor VIIa/TF inhibitory activity and a NAP domain with an amino acid sequence that is substantially the same as the NAP domain of AcaNAPc2 [SEQ. ID. NO. 59].  
30

121. A pharmaceutical composition comprising the protein of claim 73.

122. A pharmaceutical composition comprising the  
35 protein of claim 88.

123. A pharmaceutical composition comprising the protein of claim 92.

40 124. A pharmaceutical composition comprising an AcaNAPc2 protein [SEQ. ID. NO. 59].

5        125. A method of inhibiting blood coagulation  
comprising administering a protein of claim 73 with a  
pharmaceutically acceptable carrier.

10        126. A method of inhibiting blood coagulation  
comprising administering a protein of claim 88 with a  
pharmaceutically acceptable carrier.

15        127. A method of inhibiting blood coagulation  
comprising administering a protein of claim 92 with a  
pharmaceutically acceptable carrier.

20        128. A method of inhibiting blood coagulation  
comprising administering an AcaNAPc2 protein [SEQ. ID. NO.  
59].

25        129. A protein of claim 73, wherein said protein has  
two NAP domains.

30        130. A protein of claim 88, wherein said protein has  
two NAP domains.

35        131. A protein of claim 92, wherein said protein has  
two NAP domains.

40        132. An isolated protein having anticoagulant  
activity, wherein said protein specifically inhibits the  
catalytic activity of the fVIIa/TF complex in the presence  
of fXa or catalytically inactive fXa derivative, and does  
not specifically inhibit the activity of FVIIa in the  
absence of TF and does not specifically inhibit  
prothrombinase.

45        133. A protein of claim 132, wherein the protein is  
AcaNAPc2 [SEQ. ID. NO. 59].

50        134. An isolated recombinant cDNA molecule encoding a  
protein having anticoagulant activity, wherein said

5 protein specifically inhibits the catalytic activity of  
the fVIIa/TF complex in the presence of fXa or  
catalytically inactive fXa derivative, and does not  
specifically inhibit the activity of FVIIa in the absence  
of TF and does not specifically inhibit prothrombinase.

10

135. The cDNA molecule of claim 134, wherein the cDNA  
codes for AcaNAPc2 [SEQ. ID. NO. 59].

136. An isolated cDNA molecule having a nucleotide  
15 sequence substantially the same as AcaNAPc2 [SEQ. ID. NO.  
19].

137. A protein having an amino acid sequence  
substantially the same as AcaNAPc2 [SEQ. ID. NO. 59].

20

138. A protein of claim 1 wherein said NAP domain  
includes the amino acid sequence:  
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-  
Cys-A9-Cys-A10

25 wherein

- (a) Cys-A1 is selected from SEQ. ID NOS. 83 and 205;
- (b) Cys-A2-Cys is selected from one of SEQ. ID. NOS.  
206 to 208;
- (c) A3-Cys-A4 is selected from one of SEQ. ID. NOS.  
30 209 to 222.
- (d) Cys-A5 is selected from SEQ. ID. NOS. 223 and  
224;
- (e) Cys-A6 is selected from one of SEQ. ID. NOS. 225  
to 227;
- 35 (f) Cys-A7-Cys-A8 is selected from one of SEQ. ID.  
NOS. 228 to 229;
- (g) Cys-A9 is selected from one of SEQ. ID. NOS. 230  
to 232; and
- (h) Cys-A10 is selected from one of SEQ. ID. NOS.  
40 233 to 253.



5        139. An isolated protein having serine protease  
inhibitory activity and having one or more NAP domains,  
wherein each NAP domain includes the sequence:  
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-  
Cys-A9-Cys-A10 [FORMULA IV],

10        wherein

(a) A1 is an amino acid sequence of 7 to 8 amino  
acid residues;

(b) A2 is an amino acid sequence;

(c) A3 is an amino acid sequence of 3 amino acid  
15 residues;

(d) A4 is an amino acid sequence;

(e) A5 is an amino acid sequence of 3 to 4 amino  
acid residues;

(f) A6 is an amino acid sequence;

20        (g) A7 is an amino acid residue;

(h) A8 is an amino acid sequence of 10 to 12 amino  
acid residues; and

(i) A9 is an amino acid sequence of 5 to 7 amino  
acid residues;

25        (j) A10 is an amino acid sequence;

wherein each of A2, A4, A6 and A10 has an independently  
selected number of independently selected amino acid  
residues and each sequence is selected such that each NAP  
domain has in total less than about 120 amino acid  
30 residues.

140. The protein of claim 139, wherein A3 has the  
sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are  
independently selected amino acid residues.  
35

141. The protein of claim 139, wherein A3 is Glu-Pro-  
Lys.

142. The protein of claim 139, wherein A4 is an amino  
40 acid sequence having a net anionic charge.

5        143. The protein of claim 139, wherein A5 has the  
sequence A5<sub>a</sub>-A5<sub>b</sub>-A5<sub>c</sub>, wherein A5<sub>a</sub> through A5<sub>c</sub> are  
independently selected amino acid residues.

10       144. The protein of claim 143, wherein A5<sub>a</sub> is Thr and  
A5<sub>c</sub> is Asn.

145. The protein of claim 144, wherein A5 is selected  
from Thr-Leu-Asn and Thr-Met-Asn.

15       146. The protein of claim 139, wherein A7 is Gln.

147. The protein of claim 139 derived from a nematode  
species.

20       148. The protein of claim 147, wherein said nematode  
species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
*duodenale*, *Necator americanus*, and *Heligomosomoides*  
*polygyrus*.

25

149. The protein of claim 139, wherein

(a) A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and  
A3<sub>b</sub> are independently selected amino acid residues;

30       (b) A4 is an amino acid sequence having a net  
anionic charge;

(c) A5 has the sequence A5<sub>a</sub>-A5<sub>b</sub>-A5<sub>c</sub>, wherein A5<sub>a</sub>  
through A5<sub>c</sub> are independently selected amino acid  
residues; and

35       (d) A7 is Gln.

35

150. The protein of claim 149 having a NAP domain  
with an amino acid sequence that is substantially the same  
as NAP domains selected from HpoNAP5 [SEQ. ID. NO. 60] and  
NamNAP [SEQ. ID. NO. 61].

40

151. The protein of claim 149 derived from a nematode  
species.

5

152. The protein of claim 151, wherein said nematode species is selected from the group consisting of *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

153. The protein of claim 139, wherein  
(a) A3 is Glu-Pro-Lys;  
(b) A4 is an amino acid sequence having a net  
15 anionic charge;  
(c) A5 is selected from Thr-Leu-Asn and Thr-Met-Asn;  
and  
(d) A7 is Gln.

20 154. The protein of claim 153 having a NAP domain with an amino acid sequence that is substantially the same as NAP domains selected from HpoNAP5 [SEQ. ID. NO. 60] and NamNAP [SEQ. ID. NO. 61].

25 155. The protein of claim 153 derived from a nematode species.

156. The protein of claim 155, wherein said nematode species is selected from the group consisting of  
30 *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

157. An isolated protein having serine protease  
35 inhibitory activity and a NAP domain with an amino acid sequence substantially the same as NAP domains selected from the group consisting of HpoNAP5 [SEQ. ID. NO. 60] and NamNAP [SEQ. ID. NO. 61].

40 158. An isolated recombinant cDNA molecule encoding a protein having serine protease inhibitory activity and having one or more NAP domains, wherein each NAP domain

5 includes the sequence:

Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-  
Cys-A9-Cys-A10 [FORMULA IV],

wherein

- 10 (a) A1 is an amino acid sequence of 7 to 8 amino  
acid residues;  
(b) A2 is an amino acid sequence;  
(c) A3 is an amino acid sequence of 3 amino acid  
residues;  
(d) A4 is an amino acid sequence;  
15 (e) A5 is an amino acid sequence of 3 to 4 amino  
acid residues;  
(f) A6 is an amino acid sequence;  
(g) A7 is an amino acid residue;  
(h) A8 is an amino acid sequence of 10 to 12 amino  
20 acid residues;  
(i) A9 is an amino acid sequence of 5 to 7 amino  
acid residues; and  
(j) A10 is an amino acid sequence;  
wherein each of A2, A4, A6 and A10 has an independently  
25 selected number of independently selected amino acid  
residues and each sequence is selected such that each NAP  
domain has in total less than about 120 amino acid  
residues.

30 159. The cDNA molecule of claim 158, wherein A3 is an  
amino acid sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are  
independently selected amino acid residues.

160. The cDNA molecule of claim 158, wherein A3 is  
35 Glu-Pro-Lys.

161. The cDNA molecule of claim 158, wherein A4 is an  
amino acid sequence having a net anionic charge.

40 162. The cDNA molecule of claim 158, wherein A5 has  
the sequence A5<sub>a</sub>-A5<sub>b</sub>-A5<sub>c</sub>, wherein A5<sub>a</sub> through A5<sub>c</sub> are  
independently selected amino acid residues.

5

163. The cDNA molecule of claim 162, wherein A5<sub>a</sub> is Thr and A5<sub>c</sub> is Asn.

164. The cDNA molecule of claim 163, wherein A5 is  
10 selected from Thr-Leu-Asn and Thr-Met-Asn.

165. The cDNA molecule of claim 158, wherein A7 is Gln.

15 166. The cDNA molecule of claim 158 derived from a nematode species.

167. The cDNA molecule of claim 166, wherein said nematode species is selected from the group consisting of  
20 *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

168. The cDNA molecule of claim 158, wherein  
25 (a) A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are independently selected amino acid residues;

(b) A4 is an amino acid sequence having a net anionic charge;

(c) A5 is has the sequence A5<sub>a</sub>-A5<sub>b</sub>-A5<sub>c</sub>, wherein A5<sub>a</sub>  
30 through A5<sub>c</sub> are independently selected amino acid residues; and

(d) A7 is Gln.

169. The cDNA molecule of claim 168 having a  
35 nucleotide sequence substantially the same as sequences selected from cDNAs coding for HpoNAP5 [SEQ. ID. NO. 14] and NamNAP [SEQ. ID. NO. 39].

170. The cDNA molecule of claim 168 derived from a  
40 nematode species.

5           171. The cDNA molecule of claim 170, wherein said  
nematode species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
*duodenale*, *Necator americanus*, and *Heligomosomoides*  
*polygyrus*.

10

172. The cDNA molecule of claim 158, wherein

(a) A3 is Glu-Pro-Lys;

(b) A4 is an amino acid sequence having a net  
anionic charge;

15           (c) A5 is selected from Thr-Leu-Asn and Thr-Met-Asn;  
and

(d) A7 is Gln.

173. The cDNA molecule of claim 172 selected from  
20 cDNAs coding for a protein having a NAP domain with an  
amino acid sequence substantially the same as NAPs of  
HpoNAP5 [SEQ. ID. NO. 60] and NamNAP [SEQ. ID. NO. 61].

174. The cDNA molecule of claim 172 derived from a  
25 nematode species.

175. The cDNA molecule of claim 174, wherein said  
nematode species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
30 *duodenale*, *Necator americanus*, and *Heligomosomoides*  
*polygyrus*.

176. A cDNA molecule encoding a protein having serine  
protease inhibitory activity selected from the group  
35 consisting proteins having NAP domains substantially the  
same as of HpoNAP5 [SEQ. ID. NO. 60] and NamNAP [SEQ. ID.  
NO. 61].

177. A pharmaceutical composition comprising the  
40 protein of claim 139.

178. A pharmaceutical composition comprising the

5 protein of claim 149.

179. A pharmaceutical composition comprising the protein of claim 153.

10 180. A pharmaceutical composition comprising a protein selected from the group consisting of HpoNAP5 [SEQ. ID. NO. 60] and NamNAP [SEQ. ID. NO. 61].

15 181. A method of inhibiting blood coagulation comprising administering a protein of claim 139 with a pharmaceutically acceptable carrier.

20 182. A method of inhibiting blood coagulation comprising administering a protein of claim 149 with a pharmaceutically acceptable carrier.

25 183. A method of inhibiting blood coagulation comprising administering a protein of claim 153 with a pharmaceutically acceptable carrier.

30 184. A method of inhibiting blood coagulation comprising administering a protein selected from the group consisting of HpoNAP5 [SEQ. ID. NO. 60] and NamNAP [SEQ. ID. NO. 61].

185. A protein of claim 139, wherein said protein has two NAP domains.

35 186. A protein of claim 149, wherein said protein has two NAP domains.

187. A protein of claim 153, wherein said protein has two NAP domains.

40 188. A protein of claim 139 wherein said NAP domain includes the amino acid sequence:  
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-

- 5 Cys-A9-Cys-A10  
wherein
- (a) Cys-A1 is selected from SEQ. ID NOS. 86 and 254;
  - (b) Cys-A2-Cys is selected from one of SEQ. ID. NOS. 255 to 257;
  - 10 (c) A3-Cys-A4 is selected from one of SEQ. ID. NOS. 258 to 271.
  - (d) Cys-A5 is selected from SEQ. ID. NOS. 272 and 273;
  - (e) Cys-A6 is selected from one of SEQ. ID. NOS. 274
  - 15 to 276;
  - (f) Cys-A7-Cys-A8 is selected from one of SEQ. ID. NOS. 277 to 279;
  - (g) Cys-A9 is selected from one of SEQ. ID. NOS. 280 to 282; and
  - 20 (h) Cys-A10 is selected from one of SEQ. ID. NOS. 283 to 307.

189. An isolated protein having anticoagulant activity and having one or more NAP domains, wherein each
- 25 NAP domain includes the sequence:  
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 [FORMULA V],  
wherein
- 30 (a) A1 is an amino acid sequence of 7 to 8 amino acid residues;
  - (b) A2 is an amino acid sequence;
  - (c) A3 is an amino acid sequence of 3 amino acid residues;
  - (d) A4 is an amino acid sequence;
  - 35 (e) A5 is an amino acid sequence of 3 to 4 amino acid residues;
  - (f) A6 is an amino acid sequence;
  - (g) A7 is an amino acid residue;
  - (h) A8 is an amino acid sequence of 11 to 12 amino
  - 40 acid residues;
  - (i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and



5           (j) A10 is an amino acid sequence;  
wherein each of A2, A4, A6 and A10 has an independently  
selected number of independently selected amino acid  
residues and each sequence is selected such that each NAP  
domain has in total less than about 120 amino acid  
10 residues.

190. The protein of claim 189, wherein A3 has the  
sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are  
independently selected amino acid residues.

15  
191. The protein of claim 189, wherein A3 has the  
sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> is selected from the  
group consisting of Ala, Arg, Pro, Lys, Ile, His, Leu, and  
Thr, and A3<sub>b</sub> is selected from the group consisting of Lys,  
20 Thr, and Arg.

192. The protein of claim 191, wherein A3 is selected  
from the group consisting of  
Glu-Ala-Lys,  
25 Glu-Arg-Lys,  
Glu-Pro-Lys,  
Glu-Lys-Lys,  
Glu-Ile-Thr,  
Glu-His-Arg,  
30 Glu-Leu-Lys, and  
Glu-Thr-Lys.

193. The protein of claim 189, wherein A4 is an amino  
acid sequence having a net anionic charge.

35  
194. The protein of claim 189, wherein A7 is Val.

195. The protein of claim 189, wherein A7 is Ile.

40  
196. The protein of claim 189, wherein A8 includes  
the amino acid sequence A8<sub>a</sub>-A8<sub>b</sub>-A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> [SEQ.  
ID. NO. 68], wherein

- 5       (a) A8<sub>a</sub> is the first amino acid residue in A8,  
      (b) at least one of A8<sub>a</sub> and A8<sub>b</sub> is selected from the  
group consisting of Glu or Asp, and  
      (c) A8<sub>c</sub> through A8<sub>g</sub> are independently selected amino  
acid residues.

10

197. The protein of claim 196, wherein

- (a) A8<sub>a</sub> is Glu or Asp,  
      (b) A8<sub>b</sub> is an independently selected amino acid  
residue,  
15       (c) A8<sub>c</sub> is Gly,  
      (d) A8<sub>d</sub> is selected from the group consisting of  
Phe, Tyr, and Leu,  
      (e) A8<sub>e</sub> is Tyr,  
      (f) A8<sub>f</sub> is Arg, and  
20       (g) A8<sub>g</sub> is selected from Asp and Asn.

198. The protein of claim 197, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-  
A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of

- 25       Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
      Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
      Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
      Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
      Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].

30       199. The protein of claim 196, wherein

- (a) A8<sub>a</sub> is an independently selected amino acid  
residue,  
      (b) A8<sub>b</sub> is Glu or Asp,  
      (c) A8<sub>c</sub> is Gly,  
35       (d) A8<sub>d</sub> is selected from the group consisting of  
Phe, Tyr, and Leu,  
      (e) A8<sub>e</sub> is Tyr,  
      (f) A8<sub>f</sub> is Arg, and  
      (g) A8<sub>g</sub> is selected from Asp and Asn.

40

200. The protein of claim 199, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-  
A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of

5 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
10 Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].

201. The protein of claim 196, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-  
A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of

15 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].

202. The protein of claim 189, wherein A10 is  
20 includes an amino acid sequence selected from the group  
consisting of

25 Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],  
Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

203. The protein of claim 202, wherein A10 includes  
the amino acid sequence Glu-Ile-Ile-His-Val [SEQ. ID. NO.  
74].

30

204. The protein of claim 203 having a NAP domain  
with an amino acid sequence substantially the same as that  
of AcaNAP5 [SEQ. ID. NO. 40] or AcaNAP6 [SEQ. ID. NO. 41].

35 205. The protein of claim 202, wherein A10 includes  
the amino acid sequence Asp-Ile-Ile-Met-Val [SEQ. ID. NO.  
75].

40 206. The protein of claim 205 having a NAP domain  
with an amino acid sequence substantially the same as that  
of AcaNAP48 [SEQ. ID. NO. 42].

5           207. The protein of claim 202, wherein A10 includes the sequence Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76].

          208. The protein of claim 207 having a NAP domain with an amino acid sequence substantially the same as a  
10 NAP domain selected from NAP domains of AcaNAP23 [SEQ. ID. NO. 43], AcaNAP24 [SEQ. ID. NO. 44], AcaNAP25 [SEQ. ID. NO. 45], AcaNAP44 [SEQ. ID. NO. 46], AcaNAP31 [SEQ. ID. NO. 47], AceNAP4 [SEQ. ID. NOS. 48 or 49].

15           209. The protein of claim 202, wherein A10 includes the sequence Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

          210. The protein of claim 209 having a NAP domain with an amino acid sequence substantially the same as a  
20 NAP domain selected from NAP domains of AcaNAP45 [SEQ. ID. NOS. 50 or 53], AcaNAP47 [SEQ. ID. NOS. 51 or 54], AduNAP7 [SEQ. ID. NOS. 52 or 56], AduNAP4 [SEQ. ID. NO. 55], AceNAP5 [SEQ. ID. NO. 57], and AceNAP7 [SEQ. ID. NO. 58].

25           211. The protein of claim 189 derived from a nematode species.

          212. The protein of claim 211, wherein said nematode species is selected from the group consisting of  
30 *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

          213. The protein of claim 189, wherein  
35           (a) A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are independently selected amino acid residues;  
          (b) A4 is an amino acid sequence having a net anionic charge;  
          (c) A7 is selected from the group consisting of Val  
40 and Ile;  
          (d) A8 includes an amino acid sequence selected from the group consisting of

- 5 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73]; and  
10 (e) A10 includes an amino sequence selected from the  
group consisting of  
Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],  
Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
15 Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

214. The protein of claim 213 having a NAP domain  
substantially the same as a NAP domain selected from the  
group consisting of AcaNAP5 [SEQ. ID. NO. 40], AcaNAP6  
20 [SEQ. ID. NO. 41], AcaNAP48 [SEQ. ID. NO. 42], AcaNAP23  
[SEQ. ID. NO. 43], AcaNAP24 [SEQ. ID. NO. 44], AcaNAP25  
[SEQ. ID. NO. 45], AcaNAP44 [SEQ. ID. NO. 46], AcaNAP31  
[SEQ. ID. NO. 47], AceNAP4 [SEQ. ID. NOS. 48 or 49],  
AcaNAP45 [SEQ. ID. NOS. 50 or 53], AcaNAP47 [SEQ. ID. NOS.  
25 51 or 54], AduNAP7 [SEQ. ID. NOS. 52 or 56], AduNAP4 [SEQ.  
ID. NO. 55], AceNAP5 [SEQ. ID. NO. 57], and AceNAP7 [SEQ.  
ID. NO. 58].

215. The protein of claim 213 derived from a nematode  
30 species.

216. The protein of claim 215, wherein said nematode  
species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
35 *duodenale*, *Necator americanus*, and *Heligomosomoides*  
*polygyrus*.

217. The protein of claim 189, wherein  
(a) A3 is selected from the group consisting of  
40 Glu-Ala-Lys,  
Glu-Arg-Lys,  
Glu-Pro-Lys,

- 5           Glu-Lys-Lys,  
          Glu-Ile-Thr,  
          Glu-His-Arg,  
          Glu-Leu-Lys, and  
          Glu-Thr-Lys;
- 10       (b) A4 is an amino acid sequence having a net  
          anionic charge;  
          (c) A7 is Val or Ile;  
          (d) A8 includes an amino acid sequence selected from  
              the group consisting of
- 15           A8<sub>a</sub>-A8<sub>b</sub>-Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 78],  
          A8<sub>a</sub>-A8<sub>b</sub>-Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 79],  
          A8<sub>a</sub>-A8<sub>b</sub>-Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 80],  
          A8<sub>a</sub>-A8<sub>b</sub>-Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 81],  
          and
- 20           A8<sub>a</sub>-A8<sub>b</sub>-Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 82],  
          wherein at least one of A8<sub>a</sub> and A8<sub>b</sub> is Glu or Asp;  
          (e) A9 is an amino acid sequence of five amino acid  
              residues; and  
          (f) A10 includes an amino acid sequence selected
- 25       from the group consisting of  
          Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],  
          Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
          Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
          Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].
- 30
218. The protein of claim 217 having a NAP domain  
substantially the same as a NAP domain selected from the  
group consisting of AcaNAP5 [SEQ. ID. NO. 40], AcaNAP6  
[SEQ. ID. NO. 41], AcaNAP48 [SEQ. ID. NO. 42], AcaNAP23  
35 [SEQ. ID. NO. 43], AcaNAP24 [SEQ. ID. NO. 44], AcaNAP25  
[SEQ. ID. NO. 45], AcaNAP44 [SEQ. ID. NO. 46], AcaNAP31  
[SEQ. ID. NO. 47], AceNAP4 [SEQ. ID. NO. 48 or 49],  
AcaNAP45 [SEQ. ID. NO. 50 or 53], AcaNAP47 [SEQ. ID. NO.  
51 or 54], AduNAP7 [SEQ. ID. NO. 52 or 56], AduNAP4 [SEQ.  
40 ID. NO. 55], AceNAP5 [SEQ. ID. NO. 57], and AceNAP7 [SEQ.  
ID. NO. 58].

5           219. The protein of claim 217 derived from a nematode species.

          220. The protein of claim 219, wherein said nematode species is selected from the group consisting of  
10 *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma duodenale*, *Necator americanus*, and *Heligomosomoides polygyrus*.

          221. An isolated protein having anticoagulant  
15 activity selected from the group consisting of AcaNAP5 [SEQ. ID. NO. 40], AcaNAP6 [SEQ. ID. NO. 41], AcaNAP48 [SEQ. ID. NO. 42], AcaNAP23 [SEQ. ID. NO. 43], AcaNAP24 [SEQ. ID. NO. 44], AcaNAP25 [SEQ. ID. NO. 45], AcaNAP44 [SEQ. ID. NO. 46], AcaNAP31 [SEQ. ID. NO. 47], AceNAP4  
20 [SEQ. ID. NO. 62], AcaNAP45 [SEQ. ID. NO. 63], AcaNAP47 [SEQ. ID. NO. 64], AduNAP7 [SEQ. ID. NO. 65], AduNAP4 [SEQ. ID. NO. 55], AceNAP5 [SEQ. ID. NO. 57], and AceNAP7 [SEQ. ID. NO. 58].

25           222. An isolated recombinant cDNA molecule encoding a protein having anticoagulant activity and having one or more NAP domains, wherein each NAP domain includes the sequence:

Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-  
30 Cys-A9-Cys-A10 [FORMULA V],

          wherein

(a) A1 is an amino acid sequence of 7 to 8 amino acid residues;

(b) A2 is an amino acid sequence;

35 (c) A3 is an amino acid sequence of 3 amino acid residues;

(d) A4 is an amino acid sequence;

(e) A5 is an amino acid sequence of 3 to 4 amino acid residues;

40 (f) A6 is an amino acid sequence;

(g) A7 is an amino acid residue;

5 (h) A8 is an amino acid sequence of 11 to 12 amino acid residues;

(i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and

(j) A10 is an amino acid sequence;

10 wherein each of A2, A4, A6 and A10 has an independently selected number of independently selected amino acid residues and each sequence is selected such that each NAP domain has in total less than about 120 amino acid residues.

15

223. The cDNA molecule of claim 222, wherein A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are independently selected amino acid residues.

20 224. The cDNA molecule of claim 222, wherein A3 is an amino acid sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> is selected from the group consisting of Ala, Arg, Pro, Lys, Ile, His, Leu, and Thr, and A3<sub>b</sub> is selected from the group consisting of Lys, Thr, and Arg.

25

225. The cDNA molecule of claim 224, wherein A3 is selected from the group consisting of

Glu-Ala-Lys,

Glu-Arg-Lys,

30 Glu-Pro-Lys,

Glu-Lys-Lys,

Glu-Ile-Thr,

Glu-His-Arg,

Glu-Leu-Lys, and

35 Glu-Thr-Lys.

226. The cDNA molecule of claim 222, wherein A4 is an amino acid sequence having a net anionic charge.

40 227. The cDNA molecule of claim 222, wherein A7 is Val.



5        228. The cDNA molecule of claim 222, wherein A7 is Ile.

229. The cDNA molecule of claim 222, wherein A8 includes an amino acid sequence A8<sub>a</sub>-A8<sub>b</sub>-A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-  
10 A8<sub>g</sub>, [SEQ. ID. NO. 68] wherein  
      (a) A8<sub>a</sub> is the first amino acid residue in A8,  
      (b) at least one of A8<sub>a</sub> and A8<sub>b</sub> is selected from the group consisting of Glu or Asp, and  
      (c) A8<sub>c</sub> through A8<sub>g</sub> are independently selected amino  
15 acid residues.

230. The cDNA molecule of claim 229, wherein  
      (a) A8<sub>a</sub> is Glu or Asp,  
      (b) A8<sub>b</sub> is an independently selected amino acid  
20 residue,  
      (c) A8<sub>c</sub> is Gly,  
      (d) A8<sub>d</sub> is selected from the group consisting of Phe, Tyr, and Leu,  
      (e) A8<sub>e</sub> is Tyr,  
25        (f) A8<sub>f</sub> is Arg, and  
      (g) A8<sub>g</sub> is selected from Asp and Asn.

231. The cDNA molecule of claim 230, wherein A8<sub>c</sub>-A8<sub>d</sub>-A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of  
30 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].  
35

232. The cDNA molecule of claim 229, wherein  
      (a) A8<sub>a</sub> is an independently selected amino acid  
residue,  
      (b) A8<sub>b</sub> is Glu or Asp,  
40        (c) A8<sub>c</sub> is Gly,  
      (d) A8<sub>d</sub> is selected from the group consisting of Phe, Tyr, and Leu,

- 5       (e) A8<sub>e</sub> is Tyr,  
      (f) A8<sub>f</sub> is Arg, and  
      (g) A8<sub>g</sub> is selected from Asp and Asn.

233. The cDNA molecule of claim 232, wherein A8<sub>c</sub>-A8<sub>d</sub>-  
10 A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of  
      Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
      Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
      Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
      Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
15       Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].

234. The cDNA molecule of claim 229, wherein A8<sub>c</sub>-A8<sub>d</sub>-  
A8<sub>e</sub>-A8<sub>f</sub>-A8<sub>g</sub> is selected from the group consisting of  
      Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
20       Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
      Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
      Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
      Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73].

25       235. The cDNA molecule of claim 222, wherein A10  
includes an amino acid sequence selected from the group  
consisting of  
      Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],  
      Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
30       Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
      Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

236. The cDNA molecule of claim 235, wherein A10  
includes the sequence Glu-Ile-Ile-His-Val [SEQ. ID. NO.  
35 74].

237. The cDNA molecule of claim 236, having a  
nucleotide sequence substantially the same as that coding  
for AcaNAP5 [SEQ. ID. NO. 3] or AcaNAP6 [SEQ. ID. NO. 5].  
40

5           238. The cDNA molecule of claim 235, wherein A10  
includes the sequence Asp-Ile-Ile-Met-Val [SEQ. ID. NO.  
75].

239. The cDNA molecule of claim 238, having a  
10 nucleotide sequence substantially the same as that coding  
for AcaNAP48 [SEQ. ID. NO. 38].

240. The cDNA molecule of claim 235, wherein A10  
includes the sequence Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID.  
15 NO. 76].

241. The cDNA molecule of claim 240 having a  
nucleotide sequence substantially the same as that  
selected from the group consisting of cDNAs coding for  
20 AcaNAP23 [SEQ. ID. NO. 31], AcaNAP24 [SEQ. ID. NO. 32],  
AcaNAP25 [SEQ. ID. NO. 33], AcaNAP44 [SEQ. ID. NO. 35],  
AcaNAP31 [SEQ. ID. NO. 34], and AceNAP4 [SEQ. ID. NO. 9].

242. The cDNA molecule of claim 235, wherein A10  
25 includes the sequence Met-Glu-Ile-Ile-Thr [SEQ. ID. NO.  
77].

243. The cDNA molecule of claim 242 having a  
nucleotide sequence substantially the same as that  
30 selected from the group consisting of cDNAs coding for  
AcaNAP45 [SEQ. ID. NO. 36], AcaNAP47 [SEQ. ID. NO. 37],  
AduNAP7 [SEQ. ID. NO. 13], AduNAP4 [SEQ. ID. NO. 12],  
AceNAP5 [SEQ. ID. NO. 10], and AceNAP7 [SEQ. ID. NO. 11].

35           244. The cDNA molecule of claim 222 derived from a  
nematode species.

245. The cDNA molecule of claim 244, wherein said  
nematode species is selected from the group consisting of  
40 *Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
*duodenale*, *Necator americanus*, and *Heligomosomoides*  
*polygyrus*.

5

246. The cDNA molecule of claim 222, wherein

(a) A3 has the sequence Glu-A3<sub>a</sub>-A3<sub>b</sub>, wherein A3<sub>a</sub> and A3<sub>b</sub> are independently selected amino acid residues;

10 (b) A4 is an amino acid sequence having a net anionic charge;

(c) A7 is selected from the group consisting of Val and Ile;

(d) A8 includes an amino acid sequence selected from the group consisting of

15 Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 69],  
Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 70],  
Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 71],  
Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 72], and  
Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 73]; and

20 (e) A10 includes an amino sequence selected from the group consisting of

Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],  
Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],  
Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and  
25 Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

247. The cDNA molecule of claim 246 having a nucleotide sequence substantially the same as that selected from the group consisting of cDNAs coding for

30 AcaNAP5 [SEQ. ID. NO. 3], AcaNAP6 [SEQ. ID. NO. 5],  
AcaNAP48 [SEQ. ID. NO. 38], AcaNAP23 [SEQ. ID. NO. 31],  
AcaNAP24 [SEQ. ID. NO. 32], AcaNAP25 [SEQ. ID. NO. 33],  
AcaNAP44 [SEQ. ID. NO. 35], AcaNAP31 [SEQ. ID. NO. 34],  
AceNAP4 [SEQ. ID. NO. 9], AcaNAP45 [SEQ. ID. NO. 36],  
35 AcaNAP47 [SEQ. ID. NO. 37], AduNAP7 [SEQ. ID. NO. 13],  
AduNAP4 [SEQ. ID. NO. 12], AceNAP5 [SEQ. ID. NO. 10], and  
AceNAP7 [SEQ. ID. NO. 11].

248. The cDNA molecule of claim 246 derived from a  
40 nematode species.

5        249. The cDNA molecule of claim 248, wherein said  
nematode species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
*duodenale*, *Necator americanus*, and *Heligomosomoides*  
*polygyrus*.

10

250. The cDNA molecule of claim 222, wherein

(a) A3 is selected from the group consisting of

Glu-Ala-Lys,

Glu-Arg-Lys,

15

Glu-Pro-Lys,

Glu-Lys-Lys,

Glu-Ile-Thr,

Glu-His-Arg,

Glu-Leu-Lys, and

20

Glu-Thr-Lys;

(b) A4 is an amino acid sequence having a net  
anionic charge;

(c) A7 is Val or Ile;

(d) A8 is selected from the group consisting of

25

A8a-A8b-Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 78],

A8a-A8b-Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 79],

A8a-A8b-Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 80],

A8a-A8b-Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 81],

and

30

A8a-A8b-Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 82],  
wherein at least one of A8a and A8b is Glu or Asp;

(e) A9 is an amino acid sequence of five amino acid  
residues; and

(f) A10 includes an amino acid sequence selected  
35 from the group consisting of

Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],

Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],

Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and

Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].

40

251. The cDNA molecule of claim 250 that is selected  
from the group consisting of cDNAs coding for AcaNAP5

5 [SEQ. ID. NO. 3], AcaNAP6 [SEQ. ID. NO. 5], AcaNAP48 [SEQ.  
ID. NO. 38], AcaNAP23 [SEQ. ID. NO. 31], AcaNAP24 [SEQ.  
ID. NO. 32], AcaNAP25 [SEQ. ID. NO. 33], AcaNAP44 [SEQ.  
ID. NO. 35], AcaNAP31 [SEQ. ID. NO. 34], AceNAP4 [SEQ. ID.  
NO. 9], AcaNAP45 [SEQ. ID. NO. 36], AcaNAP47 [SEQ. ID. NO.  
10 37], AduNAP7 [SEQ. ID. NO. 13], AduNAP4 [SEQ. ID. NO. 12],  
AceNAP5 [SEQ. ID. NO. 10], and AceNAP7 [SEQ. ID. NO. 11].

252. The cDNA molecule of claim 250 derived from a  
nematode species.

15

253. The cDNA molecule of claim 252, wherein said  
nematode species is selected from the group consisting of  
*Ancylostoma caninum*, *Ancylostoma ceylanicum*, *Ancylostoma*  
*duodenale*, *Necator americanus*, and *Heligomosomoides*  
20 *polygyrus*.

254. A cDNA molecule encoding a protein having  
anticoagulant activity selected from the group consisting  
of cDNAs substantially the same as cDNAs coding for  
25 AcaNAP5 [SEQ. ID. NO. 3], AcaNAP6 [SEQ. ID. NO. 5],  
AcaNAP48 [SEQ. ID. NO. 38], AcaNAP23 [SEQ. ID. NO. 31],  
AcaNAP24 [SEQ. ID. NO. 32], AcaNAP25 [SEQ. ID. NO. 33],  
AcaNAP44 [SEQ. ID. NO. 35], AcaNAP31 [SEQ. ID. NO. 34],  
AceNAP4 [SEQ. ID. NO. 9], AcaNAP45 [SEQ. ID. NO. 36],  
30 AcaNAP47 [SEQ. ID. NO. 37], AduNAP7 [SEQ. ID. NO. 13],  
AduNAP4 [SEQ. ID. NO. 12], AceNAP5 [SEQ. ID. NO. 10], and  
AceNAP7 [SEQ. ID. NO. 11].

255. A pharmaceutical composition comprising a  
35 protein of claim 189.

256. A pharmaceutical composition comprising a  
protein of claim 213.

40 257. A pharmaceutical composition comprising a  
protein of claim 217.

5        258. A pharmaceutical composition comprising a  
protein having a NAP domain substantially the same as a  
NAP domain selected from the group consisting of AcaNAP5  
[SEQ. ID. NO. 40], AcaNAP6 [SEQ. ID. NO. 41], AcaNAP48  
[SEQ. ID. NO. 42], AcaNAP23 [SEQ. ID. NO. 43], AcaNAP24  
10 [SEQ. ID. NO. 44], AcaNAP25 [SEQ. ID. NO. 45], AcaNAP44  
[SEQ. ID. NO. 46], AcaNAP31 [SEQ. ID. NO. 47], AceNAP4  
[SEQ. ID. NOS. 48 or 49], AcaNAP45 [SEQ. ID. NOS. 50 or  
53], AcaNAP47 [SEQ. ID. NOS. 51 or 54], AduNAP7 [SEQ. ID.  
NO. 52 or 56], AduNAP4 [SEQ. ID. NO. 55], AceNAP5 [SEQ.  
15 ID. NO. 57], and AceNAP7 [SEQ. ID. NO. 58].

259. A method of inhibiting blood coagulation  
comprising administering a protein of claim 189 with a  
pharmaceutically acceptable carrier.

20

260. A method of inhibiting blood coagulation  
comprising administering a protein of claim 213 with a  
pharmaceutically acceptable carrier.

25        261. A method of inhibiting blood coagulation  
comprising administering a protein of claim 217 with a  
pharmaceutically acceptable carrier.

262. A method of inhibiting blood coagulation  
30 comprising administering a protein having a NAP domain  
substantially the same as NAP domains selected from the  
group consisting of AcaNAP5 [SEQ. ID. NO. 40], AcaNAP6  
[SEQ. ID. NO. 41], AcaNAP48 [SEQ. ID. NO. 42], AcaNAP23  
[SEQ. ID. NO. 43], AcaNAP24 [SEQ. ID. NO. 44], AcaNAP25  
35 [SEQ. ID. NO. 45], AcaNAP44 [SEQ. ID. NO. 46], AcaNAP31  
[SEQ. ID. NO. 47], AceNAP4 [SEQ. ID. NOS. 48 and 49],  
AcaNAP45 [SEQ. ID. NOS. 50 and 53], AcaNAP47 [SEQ. ID.  
NOS. 51 and 54], AduNAP7 [SEQ. ID. NOS. 52 and 56],  
AduNAP4 [SEQ. ID. NO. 55], AceNAP5 [SEQ. ID. NO. 57], and  
40 AceNAP7 [SEQ. ID. NO. 58].

263. A protein of claim 189, wherein said protein has

5 two NAP domains.

264. A protein of claim 213, wherein said protein has two NAP domains.

10 265. A protein of claim 217, wherein said protein has two NAP domains.

266. A protein having two NAP domains, wherein said protein is selected from the group consisting of AceNAP4  
15 [SEQ. ID. NO. 62], AcaNAP45 [SEQ. ID. NO. 63], AcaNAP47 [SEQ. ID. NO. 64], and AduNAP7 [SEQ. ID. NO. 65].

267. A protein of claim 1 wherein said NAP domain includes the amino acid sequence:

20 Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10

wherein

(a) Cys-A1 is selected from SEQ. ID NOS. 87 and 308;

(b) Cys-A2-Cys is selected from one of SEQ. ID. NOS.  
25 309 to 311;

(c) A3-Cys-A4 is selected from one of SEQ. ID. NOS. 312 to 325.

(d) Cys-A5 is selected from SEQ. ID. NOS. 326 and 327;

30 (e) Cys-A6 is selected from one of SEQ. ID. NOS. 328 to 330;

(f) Cys-A7-Cys-A8 is selected from SEQ. ID. NOS. 331 and 332;

(g) Cys-A9 is selected from one of SEQ. ID. NOS. 333  
35 to 335; and

(h) Cys-A10 is selected from one of SEQ. ID. NOS. 336 to 356.

268. An oligonucleotide comprising a nucleotide  
40 sequence selected from

YG109: TCAGACATGT-ATAATCTCAT-GTTGG [SEQ. ID. NO.

Added B1